

Inventors: Al-Obeidi et al.  
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which is a continuation of prior application serial no. 08/428,404, filed April 25, 1995, which is a continuation-in-part of prior application serial no. 08/233,054, filed April 26, 1994, all of which are incorporated herein by reference.

A "marked" version of this paragraph that shows the actual amendments is included as Appendix A.

#### **In The Claims**

~~Please cancel claims 1, and 12 to 19.~~

~~Please insert the following amended claims in the specification.~~

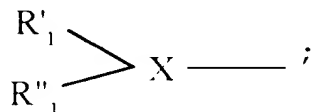
2. (amended) A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula  $A_1-A_2-(A_3)_m-B$ , wherein m is 1;

wherein  $A_1$  is  $R_1-R_2-R_3$ ;  $A_2$  is  $R_4-R_5-R_6$ ;  $A_3$  is  $R_7-R_8-R_9$ ;

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wherein

$R_1$  is



X is N;

$R'_1$  is selected from the group consisting of isobutyl, 2-methylpentyl, cyclohexylmethyl, cyclohexenylmethyl, 2-methylbutyl, -H and 2,3-dimethylpentyl;

$R''_1$  is selected from the group consisting of 2-benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzylimidazolyl, 2-naphthylmethyl, 5-pyridiminoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, 2-furoyl, 3,4-dichlorobenzoyl, 2-thienylacetyl, N(5-methyl-2-thienyl), ethoxycarbonyl, 2-fluorobenzoyl, t-butoxycarbonyl, benzyl and 1-20 amino acids;

$F_1$  is  $-CF_{2A}R_{2B}-$ , wherein  $-R_{2A}$  and  $-R_{2B}$  are independently selected from the group consisting of -H, 4-amidinophenylmethyl, 4-aminophenylmethyl, 4-hydroxyphenylmethyl, 2-naphthylmethyl,

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4-(N-methylpyridinyl)methyl,  
(3-iodo-4-aminophenyl)methyl,  
(4-aminocarbonylphenyl)methyl,  
(3-iodo-4-hydroxyphenyl)methyl, and  
(4-cyanophenyl)methyl, (4-hydroxyphenyl)methyl;

$F_3$  is  $-C(O)-$ ;

$F_4$  is  $-NH-$ ;

$F_5$  is  $-CP_{5A}R_{5B}$ , wherein  $-R_{5A}$  and  $-R_{5B}$  are independently selected from the group consisting of  $-H$ , 2-butyl, and cyclohexyl;

$F_6$  is  $-C(O)-$ ;

$F_7$  is  $-NH-$ ;

$F_8$  is  $-CP_{8A}R_{8B}$ , wherein  $-R_{8A}$  and  $-R_{8B}$  are independently selected from the group consisting of  $-H$ , 3-guanylpropyl, (dimethylamidinium)aminomethyl, (dimethylamidinium)aminoethyl, 3-(N-methylpyridinyl)methyl, and 4-(N-methylpyridinyl)methyl;

$F_9$  is  $-C(O)-$ ; and

$E$  is Leu-Pro-NH<sub>2</sub>, Leu-Hyp-NH<sub>2</sub>, Pen(CH<sub>2</sub>COOH)-Pro-NH<sub>2</sub>, Cys(CH<sub>2</sub>COOH)-Pro-NH<sub>2</sub>,  $\gamma$ -carboxyglutamic

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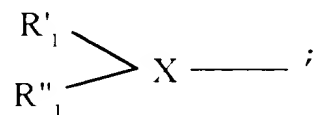
acid-Pro-NH<sub>2</sub>, (N-carboxymethyl)Gly-Pro-NH<sub>2</sub>,  
(N-carboxyethyl)Gly-Pro-NH<sub>2</sub>,  
(N-1,3-dicarboxypropyl)Gly-Pro-NH<sub>2</sub>,  
(N-methyl)Leu-Pro-NH<sub>2</sub>, Leu-NH<sub>2</sub>, Leu-OH,  
-NH-(4-trimethylammoniumbenzyl),  
-NH-[4-(1-methylpyridinium)methyl], and  
-NH-(4-amidinobenzyl).

3. (amended) A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula A<sub>1</sub>-A<sub>2</sub>-(A<sub>3</sub>)<sub>m</sub>-B, wherein m is 1;

wherein A<sub>1</sub> is R<sub>1</sub>-R<sub>2</sub>-R<sub>3</sub>; A<sub>2</sub> is R<sub>4</sub>-R<sub>5</sub>-R<sub>6</sub>; A<sub>3</sub> is R<sub>7</sub>-R<sub>8</sub>-R<sub>9</sub>;

wherein

R<sub>1</sub> is



X is N;

R'<sub>1</sub> is selected from the group consisting of H,  
isobutyl, 2-methylpentyl, cyclohexylmethyl,  
3-quinolinyl, 2-methylbutyl, 2,3 dimethyl pentyl,  
and cyclohexenylmethyl;

R''<sub>1</sub> is selected from the group consisting of 2-

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benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzimidazolyl, 2-naphthylmethyl, 5-pyrazinoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, and benzyl;

$R_2$  is  $-CR_{2A}R_{2B}$ , wherein  $-R_{2A}$  and  $-R_{2B}$  are independently selected from the group consisting of H, 3-amidinophenylmethyl, 4-amidinophenylmethyl, 4-aminophenylmethyl, 4-hydroxyphenylmethyl, 2-naphthylmethyl, 4-(N-methylpyridinyl)methyl, (3-iodo-4-aminophenyl)methyl, (4-aminocarbonylphenyl)methyl, (3-iodo-4-hydroxyphenyl)methyl, (4-cyanophenyl)methyl, and 3-indolylmethyl;

$R_3$  is selected from the group consisting of  $-C(O)-$ ,  $-CH_2-$ ,  $-CHR_{35}-C(O)-$  and  $-C(O)-NR_{35}-CH_2-C(O)-$ , wherein  $R_{35}$  is the  $CHR_{55}$  group of the bridging group  $-C(O)-CR_{55}-$ ;

$R_4$  is  $-NH-$ ;

$R_5$  is  $-CR_{5A}R_{5B}$ , wherein  $-R_{5A}$  and  $-R_{5B}$  are independently selected from the group consisting of  $-H$ , 2-butyl, cyclohexyl and phenyl;

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$R_1$  is  $-C(O)-$ ;

$R_2$  is  $-NH-$ ;

$R_3$  is  $-CR_{3A}R_{3B}$ , wherein  $-R_{3A}$  and  $-R_{3B}$  are independently selected from the group consisting of  $-H$ , 3-guanypropyl, (dimethylamidinium)aminomethyl, (dimethylamidinium)aminoethyl, 3-(N-methylpyridinyl)methyl, N(carboxymethyl)(3-pyridinylmethyl), and 4-(N-methylpyridinyl)methyl;

$R_4$  is selected from the group consisting of  $-C(O)-$ ,  $-CH_2-$  and  $-CHR_{4g}-C(O)-$ ; and

$B$  is  $-NH_2$ ,  $-OH$ , Leu-Pro- $NH_2$ , Leu-Hyp- $NH_2$ , Pen( $CH_2COOH$ )-Pro- $NH_2$ , Cys( $CH_2COOH$ )-Pro- $NH_2$ ,  $\gamma$ -carboxyglutamic acid-Pro- $NH_2$ , (N-carboxymethyl)Gly-Pro- $NH_2$ , (N-carboxyethyl)Gly-Pro- $NH_2$ , (N-1,3-dicarboxypropyl)Gly-Pro- $NH_2$ , (N-methyl)Leu-Pro- $NH_2$ , Leu- $NH_2$ , and Leu-OH.

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11. (amended) A compound selected from the group consisting of

Alloc-pAph-Chg-Pal(3)Me-NH<sub>2</sub>;  
(2-quinolinoyl)-pAph-Chg-Pal(3)Me-NH<sub>2</sub>;  
Ac-pAph-Chg-Pal(3)Me-NH(1-methoxycarbonyl)  
-1-cyclohexyl;  
Ac-pAph-Chg-Arg-NH<sub>2</sub>;  
(2-pyridoyl)-pAph-Chg-Pal(3)Me-NH<sub>2</sub>;  
CF<sub>3</sub>C(O)-(iBu)Phe(pNH<sub>2</sub>)-Chg-Arg-NH<sub>2</sub>;  
Ac-pAph-Chg-Pal(3)Me-NH-(1-methoxycarbonyl)  
-1-cyclopentyl;  
Ac-pAph-Chg-Pal(3)Me-NH-(4-methoxycarbonyl  
-cyclohexyl)methyl;  
Ac-pAph-Chg-Pal(3)Me-NH-(3-thienyl-2  
-carboxylic acid methyl ester);  
Ac-pAph-Chg-Arg-NH<sub>2</sub>;  
CF<sub>3</sub>C(O)-(iBu)Tyr-Chg-Arg-OH;  
Ac-pAph-Chg-Pal(3)Me-NH-(4-methoxycarbonyl  
-cyclohexyl)methyl;  
Ac-pAph-Chg-Pal(3)Me-NH<sub>2</sub>;  
Ac-pAph-Chg-Pal(3)(CH<sub>2</sub>COOH)-NH<sub>2</sub>;  
(2-quinolinecarboxy)-pAph-Chg-Pal(3)Me-NH<sub>2</sub>;  
Ac-pAph-Chg-Pal(3)Me-NH-(4-carboxycyclohexyl)  
methyl; and  
CF<sub>3</sub>C(O)(iBu)-Tyr-Ile-Arg-NH<sub>2</sub>.

21. (amended) A compound Ac-D-pAph-Chg-Pal(3)Me-Leu-Pro-NH<sub>2</sub>.